

Remarks

Claims 54-67, 75-92, 102-107, 115-119 and 122-175 remain pending in the instant application.

Availability of Reference Prior to Final Rejection and Applicant's Last Submission

The Examiner asserts in the Advisory Action that the exhibit (Aitkenhead *et al.* Microvasc. Res., 63:159-174 (2002)) submitted with Applicants' last response was not considered because "[t]he reference was available prior to the final rejection and prior to Applicant's last submission, therefore it is not timely filed." *See* Paper 39, Point 5. Applicants respectfully disagree.

The Aitkenhead reference was not available prior to Applicants' previous submission, as shown by the following facts. On December 19, 2001, Applicants timely filed a Response and Amendment Under 37 C.F.R. § 1.111 to Paper No. 31. *See* copy of date stamped receipt card, submitted herewith as Exhibit A. On May 7, 2002, the Examiner indicated to the undersigned Attorney for Applicants by telephone that the Response and Amendment Under 37 C.F.R. § 1.111 to Paper No. 31 was missing from the PTO files. Applicants' representative sent, by facsimile, a copy of the Response and Amendment to the Examiner. *See* copy of confirmation report of facsimile sent on May 7, 2002, submitted herewith as Exhibit B. Thus, the Response and Amendment Under 37 C.F.R. § 1.111 to Paper No. 31 was originally filed and submitted on December 19, 2001.

The Aitkenhead reference was first published online on January 23, 2002. *See* Aitkenhead *et al.* (2002), page 159. The Aitkenhead reference was not available to Applicants prior to their December 19, 2001 submission. Applicants submitted the Aitkenhead reference in response to the Examiner's final rejection dated July 15, 2002. Therefore, the Examiner's assertion that the Aitkenhead reference was available prior to Applicants' submission of December 19, 2001 is incorrect. In light of the evidence provided, Applicants respectfully request that the Examiner acknowledge the Aitkenhead reference as timely filed and reconsider the reply filed October 15, 2002, including the discussion of the relevance of the Aitkenhead reference to the rejection under 35 U.S.C. § 101.

New Issues Raised by the Examiner in the Final Rejection

The Examiner asserts in the Advisory Action that the “exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.” *See* Paper 39, Point 6. Applicants respectfully disagree.

In the final rejection dated July 15, 2002, the Examiner rejected the pending claims under 35 U.S.C. §§ 101 and 112 for allegedly lacking both utility and enablement. In support of the utility rejection, the Examiner asserted generally that: 1) the instant application allegedly does not disclose the biological role of VIGF; and 2) Applicants’ assertion that the specification discloses a function for VIGF is not persuasive since the assertion is not based on facts or evidence.

According to the Examiner’s final rejection, the Bechard (2001) reference previously cited by Applicants did not support Applicants’ asserted utility. The Examiner argued that the asserted utility of VIGF as a diagnostic for cancer was not credible in light of Bechard (2001). *See* Paper No. 35, page 4. Finally, the Examiner asserted, “there is not a reasonable correlation between the asserted uses and the activities which are described by the Bechard et al. references. There is no evidence that the claimed protein could be used as a tumor diagnostic” *See* Paper No. 35, page 5. Thus, in the final Office Action, the Examiner newly raised the issue of whether the Bechard (2001) reference supports Applicants’ asserted utility as a cancer diagnostic.

In order to rebut the Examiner’s position, Applicants submitted the Aitkenhead reference as new evidence supporting the use of VIGF as a tumor diagnostic and as evidence to overcome the Examiner’s doubts about the Bechard (2001) reference. The Response submitted October 15, 2002 used the Aitkenhead reference only to address the Examiner’s new arguments. Therefore, Applicants respectfully submit that the Aitkenhead reference did not raise new issues and request that the Examiner consider the Aitkenhead reference and the previous request for reconsideration, and request withdrawal of the rejections under 35 U.S.C. §§ 101 and 112.

Utility Asserted in the Specification and the Nexus Between VIGF and Cited Art

The Examiner asserts in the Advisory Action that “Applicant’s arguments still do not support a specific assertion of utility which has support in the specification as originally filed.” *See* Paper 39, Point 5. Applicants respectfully disagree.

The specification explicitly teaches several specific and substantial utilities for VIGF polynucleotides and polypeptides, including their use as diagnostic markers for tumors. The specification states:

VIGF protein expression may be linked to vascular disease or neovascularization associated with tumor formation. VIGF has a signal peptide and the mRNA is highly expressed in endothelial cells and to a lesser extent in smooth muscle cells which indicates that the protein is present in serum. Accordingly, an anti-VIGF antibody could be used to diagnose vascular disease or neovascularization associated with tumor formation since an altered level of this polypeptide may be indicative of such disorders.

See page 27, line 33 to page 28, line 6. Applicants assert that the disclosure that VIGF promotes “neovascularization associated with tumor formation” represents a specific assertion of utility in cancer diagnosis, particularly when viewed in the context of knowledge in the art at the time of filing. More particularly, it was widely understood that genes whose expression promotes angiogenesis are often upregulated in tumors and thus it was widely accepted that such genes are useful as cancer diagnostics. See Exhibits C-E.

Moreover, Applicants point out that the asserted utility is further supported by data published after the effective filing date of the captioned application. Both Bechard *et al.* (2001) and Aitkenhead *et al.* (2002) demonstrate that VIGF is useful as a marker for angiogenesis and carcinomas as asserted by the Applicants. As detailed in the Applicants’ response dated October 15, 2002, both references clearly provide a nexus between VIGF and angiogenesis/cancer. Specifically, the Aitkenhead reference indicates that there is “a strong correlation between ESM-1 expression and degree of vascularity. We also found very similar correlations between ESM-1 levels and markers for angiogenesis in tumors from breast, uterus, stomach and rectum ..., indicating that ESM-1 is likely expressed in the vasculature of these tumors also.” See Aitkenhead *et al.* (2002), page 166, first column. Data from the Bechard (2001) reference further support the utility asserted in the specification. This reference discloses that “the concentration of endocan was found to be elevated in the sera of patients with lung tumors.” See Bechard *et al.* (2001), page 48348, second column.¹ Thus, independent, third party research entities have confirmed the Applicants’ asserted utilities. Therefore, based on the totality of the evidence, Applicants submit that one of ordinary skill in the art would find it, more likely than not, true that the asserted utilities for the claimed

¹ The Examiner asserts that the higher levels of ESM-1 found in septic patients undercuts the credibility of using VIGF (ESM-1) to detect cancer. However, it is highly unlikely that a physician would find it necessary to resort to molecular markers to distinguish between a septic patient and a cancer patient. Thus, levels of VIGF in septic patients are not relevant to cancer diagnosis.

invention are credible, specific and substantial.

In addition, the Examiner asserted “neither the instant specification nor the prior art provides a necessary correlation or nexus between the claimed protein and any tumor which would be required for use of the claimed protein in a diagnostic capacity.” *See* Paper No. 35, page 4. Applicants respectfully disagree. The nexus between VIGF and tumors is angiogenesis. The correlation between angiogenesis and cancer biology was well established at the time the application was filed. Indeed, it has been long known in the art that angiogenesis is required for the neovascularization of tumors, their growth and invasiveness. Applicants submit herewith several abstracts of review articles that demonstrate the relationship of angiogenesis and cancer biology. *See* Exhibits F-I. The abstracts describe the association of angiogenesis and factors that modulate angiogenesis with tumor neovascularization. In addition, the prospect of inhibiting angiogenesis to treat cancers was discussed in 1991. *See* Exhibit I. Furthermore, as mentioned earlier, the use of angiogenic factors in cancer diagnosis and prognosis was likewise well known. *See* Exhibits C-E. Thus, at the time the instant application was filed, the nexus between cancer and proteins which promote angiogenesis was clear.

Scientific evidence may be used to corroborate Applicants’ asserted utility. Legal precedent for the use of post-filing date references in this manner can be found in In re Brana, where the courts stated:

The Kluge declaration, though dated after applicants’ filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. In re Marzocchi, 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4.

See In re Brana, 51 F.3d 1560 at 1567 n.19 (Fed. Cir. 1995).

Applicants contend that, contrary to the Examiner’s allegations, the specification clearly provides at least one specific, substantial, and credible asserted utility. In addition, Applicants have provided evidence from third party research entities in support of the asserted utility. In particular, Applicants have provided evidence that the polynucleotides and polypeptides of the instant application are useful as tumor diagnostics. This utility asserted in the specification for VIGF is indeed specific, substantial and credible.

Applicants further assert that only one credible assertion of utility for the claimed invention is necessary to satisfy 35 U.S.C. §§ 101 and 112; additional statements of utility, even if not “credible,” do not render the claimed invention lacking in utility. *See Raytheon v. Roper*, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835

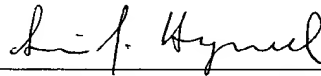
(1984). Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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